Docket No. 247788US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Hirofumi YAMAMOTO, et al. GAU:

SERIAL NO: New Application EXAMINER:

FILED: Herewith

FOR: INHIBITOR OF COX

REQUEST FOR PRIORITY

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

☐ Full benefit of the filing date of U.S. Application Serial Number , filed , is claimed pursuant to the provisions of **35 U.S.C. §120**.

☐ Full benefit of the filing date(s) of U.S. Provisional Application(s) is claimed pursuant to the provisions of **35 U.S.C. §119(e)**: **Application No.** **Date Filed**

■ Applicants claim any right to priority from any earlier filed applications to which they may be entitled pursuant to the provisions of **35 U.S.C. §119**, as noted below.

In the matter of the above-identified application for patent, notice is hereby given that the applicants claim as priority:

COUNTRY	APPLICATION NUMBER	MONTH/DAY/YEAR
Australia	2003900207	January 17, 2003
Australia	2003901873	March 31, 2003

Certified copies of the corresponding Convention Application(s)

■ are submitted herewith

☐ will be submitted prior to payment of the Final Fee

☐ were filed in prior application Serial No. filed

☐ were submitted to the International Bureau in PCT Application Number
Receipt of the certified copies by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

☐ (A) Application Serial No.(s) were filed in prior application Serial No. filed ; and

☐ (B) Application Serial No.(s)

☐ are submitted herewith

☐ will be submitted prior to payment of the Final Fee

Respectfully Submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration No. 24,618

C. Irvin McClelland
Registration Number 21,124

Customer Number
22850

Tel. (703) 413-3000
Fax. (703) 413-2220
(OSMMN 05/03)

Patent Office
Canberra

I, LEANNE MYNOTT, MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003900207 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 17 January 2003.

WITNESS my hand this
Tenth day of December 2003

LEANNE MYNOTT
MANAGER EXAMINATION SUPPORT
AND SALES

Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"New Compounds"

The invention is described in the following statement:

D E S C R I P T I O N

New compounds

Technical Field

This invention relates to new compounds having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

Background Art

The presence of two cyclooxygenase isoenzymes, cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX-II) is known (Proc. Nat. Acad. Sci. USA 88, 2692-2696 (1991)).

Traditional non steroidal anti-inflammatory compounds (NSAIDs) have inhibiting activities of both COX-I and COX-II (J. Biol. Chem., 268, 6610-6614 (1993), etc). The therapeutic use thereof involves undesired effects on the gastrointestinal tract, such as bleeding , erosions, gastric and intestinal ulcers, etc.

It was reported that selective inhibition of COX-II shows anti-inflammatory and analgesic activities comparable with conventional NSAIDs but with a lower incidence of some gastrointestinal undesired effects (Pro. Nat. Acad. Sci. USA, 91, 3228-3232(1994)). Accordingly, various selective COX-II inhibitors have been prepared. However, it was reported that those "selective COX-II inhibitor" show some side-effects on kidney and/or insufficient efficacy on acute pains.

Further, some compounds such as SC-560, mofezolac, etc, which have certain selective inhibiting activity against COX-I. WO98/57910 shows some compounds having such activity. However, their selectivity of inhibiting COX -I does not seem to be enough to use them as a clinically acceptable and satisfactory analgesic agent due to their gastrointestinal disorders.

WO02/055502 shows some pyridine derivatives having cyclooxygenase inhibiting activity, particularly cyclooxygenase-I inhibiting activity. And WO99/51580 shows some

triazole derivatives having an inhibiting activity of cytokine production.

Disclosure of Invention

This invention relates to new compounds, which have pharmaceutical activity such as cyclooxygenase (hereinafter described as COX) inhibiting activity, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

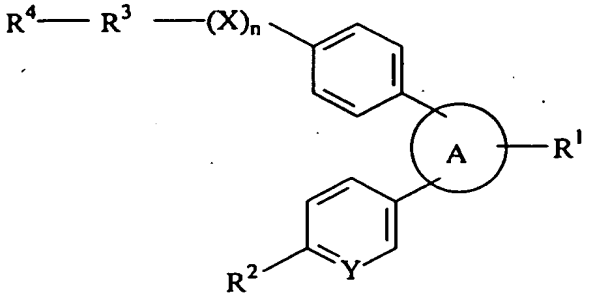
Accordingly, one object of this invention is to provide the new compounds, which have a COX inhibiting activity.

Another object of this invention is to provide a process for production of the new compounds.

A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the new compounds.

Still further object of this invention is to provide a use of the new compounds for manufacturing a medicament for treating or preventing various diseases.

The new compounds of this invention can be represented by the following general formula (I):



(I)

wherein R^1 is lower alkyl which is optionally substituted with suitable substituent(s), cyclo(lower)alkyl, lower alkynyl, cyano, acyl, or N,N-di(lower)alkylcarbamoyl;

R^2 is lower alkyl, lower alkoxy, cyano or 1H-pyrrol-1-yl;

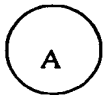
R^3 is lower alkylene or lower alkenylene;

R^4 is hydroxy, protected hydroxy, amino, protected amino, carboxy, protected carboxy, acyl, or cyano;

X is O, S, SO or SO_2;

Y is CH or N;

n is 0 or 1; and



is a N and O-containing heterocyclic group;

or salts thereof.

The object compound (I) of the present invention can be prepared by a similar manner to those of Preparations and/or Examples mentioned below.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compounds of the formula (I) and its salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "lower alkyl", and lower alkyl moiety in the term "lower alkoxy" may be a straight or branched one, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl or the like, in which preferable one is methyl or dimethyl.

Suitable lower alkoxy is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, or the like, in which preferable one is methoxy.

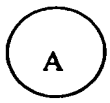
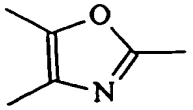
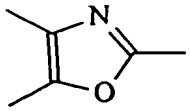
Suitable "halogen" may be fluoro, chloro, bromo or iodo or the like, which preferable one is fluoro.

Suitable "lower alkyl substituted with halogen" may be lower alkyl substituted with one or more halogen atoms(s), such as fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, or the like. And its preferable one is halogen-substituted C1-C2 alkyl. More preferable one is fluorine-substituted methyl, and most preferable one is trifluoromethyl or 2,2,2-trifluoroethyl.

Suitable "cyclo(lower)alkyl" may include 3 to 8-membered cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, preferably one having 5 to 7 carbon atoms.

Suitable "N,N-di(lower)alkylcarbamoyl" may be a carbamoyl group substituted with the same or different above lower alkyl groups on nitrogen atom, such as dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, or the like. It is preferably di(C1-C4)carbamoyl, more preferably di(C1-C2 alkyl)carbamoyl.

Suitable alkynyl may be a monovalent branched or unbranched hydrocarbon radical containing at least one carbon-carbon triple bond, for example ethynyl, 2-propynyl, 2-butynyl, and the like.

Suitable  is  or 

Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

The processes for preparing the object compounds are explained in detail in the following.

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the compounds (I) are shown in the following.

[A] ANALGESIC ACTIVITY:

Effect on adjuvant arthritis in rats:

(i) Test Method:

Arthritis was induced by injection of 0.5 mg of Mycobacterium tuberculosis (Difco Laboratories, Detroit, Mich.) in 50 μl of liquid paraffin into the right hind footpad of Lewis rats aged 7 weeks. Analgesic activity of a single dose of agents in arthritic rats was studied. Arthritic rats were randomized and grouped (n=10) for drug treatment based on pain threshold of left hind paws and body weight on day 22. Drugs (Test compounds) were administered

and the pain threshold was measured 2hr after drug administration. The intensity of hyperalgesia was assessed by the method of Randall - Selitto. The mechanical pain threshold of the left hind paw (uninjected hind paw) was determined by compressing the ankle joint with a balance pressure apparatus (Ugo Basile Co. Ltd., Varese, Italy). The threshold pressure of rats squeaking or struggling was expressed in grams. The threshold pressure of rats treated with drugs was compared with that of non-treated rats. A dose showing the ratio of 1.5 is considered to be the effective dose.

(ii) Test Results:

[B] Inhibiting activity against COX-I and COX-II (Whole Blood Assay):

(i) Test Method:

Whole blood assay for COX-I

Fresh blood was collected by syringe without anticoagulants from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection. 500 μl aliquots of human whole blood were immediately incubated with 2 μl of either DMSO vehicle or a test compound at final concentrations for 1hr at 37C to allow the blood to clot. Appropriate treatments (no incubation) were used as blanks. At the end of the incubation, 5 μl of 250mM Indomethacin was added to stop the reaction. The blood was centrifuged at 6000 x g for 5min at 4C to obtain serum. A 100 μl aliquot of serum was mixed with 400 μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4C and was assayed for TXB2 using an enzyme immunoassay kit according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of TXB2 production relative to control incubations containing DMSO vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC50 value was calculated by least squares method.

Whole blood assay for COX-II

Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection. 500μl aliquots of human whole blood were incubated with either 2μl DMSO vehicle or 2 μl of a test compound at final concentrations for 15min at 37C. This was followed by incubation of the blood with 10μl of 5mg/ml lipopolysaccharide for 24hr at 37C for induction of COX-2. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000 x g for 5min at 4C to obtain plasma. A 100μl aliquot of plasma was mixed with 400μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4C and was assayed for PGE2 using a radioimmunoassay kit after conversion of PGE2 to its methyl oximate derivative according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of PGE2 production relative to control incubations containing DMSO vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC50 value was calculated by least squares method.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC50 (μM)	COX-II IC50 (μM)
3	< 0.01	> 0.1
4	< 0.01	> 0.1
5	< 0.01	> 0.1

It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

[C] Inhibiting activity on aggregation of platelet

(i) Methods

Preparation of platelet-rich plasma

Blood from healthy human volunteers was collected into plastic vessels containing 3.8% sodium citrate (1/10 volume). The subject had no taken any compounds for at least seven days prior to blood collection. Platelet-rich plasma was obtained from the supernatant fraction of blood after centrifugation at 1200 r.p.m. for 10 min. Platelet-poor plasma was obtained by centrifugation of the remaining blood at 3000 r.p.m. for 10 min.

Measurement of platelet aggregation

Platelet aggregation was measured according to the turbidimetric method with an aggregometer (Hema Tracer). In the cuvette, platelet-rich plasma was pre-incubated for 2 min at 37C after the addition of compounds or vehicle. In order to quantify the inhibitory effects of each compound, the maximum increase in light transmission was determined from the aggregation curve for 7 min after the addition of agonist. We used collagen as agonist of platelet aggregation in this study. The final concentration of collagen was 0.5μg/mL. The effect of each compound was expressed as percentage inhibition agonist- induced platelet aggregation compared with vehicle treatment. Data are presented as the mean ± S.E.M. for six experiments. The IC_{50} value was obtained by linear regression, and is expressed as the compound concentration required to produce 50% inhibition of agonist-induced platelet aggregation in comparison to vehicle treatment.

It appeared, from the above-mentioned Test Result, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against platelet aggregation. Therefore, the compound (I) or pharmaceutically acceptable salts thereof are useful for preventing or treating disorders induced by platelet aggregation, such as thrombosis.

Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc.

The object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX inhibiting activity and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX mediated diseases, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, scapulohumeral periarthritis, cervical syndrome, etc.]; lumbago;
inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.];
inflammatory eye condition [e.g. conjunctivitis, etc.];
lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.];
condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.]; gingivitis; menorrhalgia;
inflammation, pain and tumescence after operation or injury [pain after odontectomy, etc] ;

pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor,
systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, or the like.

Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

The object compound (I) and a salt thereof can be used for prophylactic and therapeutic treatment of arterial thrombosis, arterial sclerosis, ischemic heart diseases[e.g. angina pectoris (e.g. stable angina pectoris, unstable angina pectoris including imminent infarction, etc.), myocardial infarction (e.g. acute myocardial infarction, etc.), coronary thrombosis, etc.], ischemic brain diseases [e.g. cerebral infarction (e.g. acute cerebral thrombosis, etc.), cerebral thrombosis (e.g. cerebral embolism, etc.), transient cerebral ischemia (e.g. transient ischemic attack, etc.), cerebrovascular spasm after cerebral hemorrhage(e.g. cerebrovascular spasm after subarachnoid hemorrhage, etc.), etc.], pulmonary vascular diseases (e.g. pulmonary thrombosis, pulmonary embolism etc.), peripheral circulatory disorder [e.g. arteriosclerosis obliterans, thromboangiitis obliterans (i.e. Buerger's disease), Raynaud's disease, complication of diabetes mellitus (e.g. diabetic angiopathy, diabetic neuropathy, etc.), phiebothrombosis (e.g. deep vein thrombosis, etc.), etc.], complication of tumors (e.g. compression thrombosis), abortion [e.g. placental thrombosis, etc.],
restenosis and reocclusion [e.g. restenosis and/or reocclusion after percutaneous transluminal coronary angioplasty (PTCA),

restenosis and reocclusion after the administration of thrombolytic drug (e.g. tissue plasminogen activator (TPA), etc.)],
thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation [e.g. surgery (e.g. open heart surgery, pump-oxygenator, etc.) hemodialysis, etc.] or transplantation, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia, essential thrombocytosis, inflammation (e.g. nephritis, etc.), immune diseases,
atrophic thrombosis, creeping thrombosis, dilation thrombosis, jumping thrombosis, mural thrombosis, etc.

The object compound (I) and a salt thereof can be used for the adjuvant therapy with thrombolytic drug (e.g. TPA, etc.) or anticoagulant (e.g. heparin, etc.).

And, the compound (I) is also useful for inhibition of thrombosis during extra corporeal circulation such as dialysis.

Particularly, the following diseases are exemplified: pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis, etc; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury; etc.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting, or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

For therapeutic purpose, the analgesic agent of the present invention can be used in a form of pharmaceutical preparation suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like.

Particularly, the analgesic agent of this invention is useful for treating or preventing acute or chronic pains associated with acute or chronic inflammations in human beings or animals by using administered systemically or topically.

The patents, patent applications and publications cited herein are incorporated by reference.

The following Preparations and Examples are given for the purpose of illustrating the present invention in detail.

Preparation 1

To a solution of 2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone (1.0 g, 3.89 mmol) in dichloromethane (10 mL) were added pyridinium tribromide (1.37 g, 4.28 mmol) and hydrogen bromide (33% solution in acetic acid, 1 mL) at ambient temperature under nitrogen and the mixture was stirred at same temperature for 40 minutes. The reaction mixture was evaporated in vacuo and acetic acid was azeotropically removed with toluene. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and

evaporated in vacuo to give
2-bromo-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl) ethanone (1.32 g, 101%) as an oil.
1H-NMR (300 MHz, CDCl3) δ 3.80 (3H, s),3.99 (3H, s),6.29 (1H, s),6.77 (1H, d, J=8 Hz),6.90 (2H, d, J=8 Hz),7.45 (2H, d, J=8 Hz),8.16 (1H, dd, J=8,2 Hz),8.80 (1H, d, J=2 Hz);

Preparation 2
To a solution of
1-[4-(benzyloxy)phenyl]-2-bromo-2-(4-methoxyphenyl)ethanone (20.65 g, 50.2 mmol) in N,N-dimethylformamide (200 mL) was added potassium phthalimide (9.3 g, 50.2 mmol) at 0℃ and the mixture was stirred at same temperature for 2 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid , water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was triturated with ethanol to give
2-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione (20.47 g, 85.4%) as a powder.
1H-NMR (300 MHz, CDCl3) δ 3.77 (3H, s),5.07 (2H, s),6.70 (1H, s),6.85 (2H, d, J=8 Hz),6.91 (2H, d, J=8 Hz),7.30-7.47 (7H, m),7.65-7.73 (2H, m),7.78-7.88 (4H, m).

Preoaration 3
To a suspension of
2-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione (20.47 g, 42.9 mmol) in ethanol (200 mL) was added hydrazine monohydrate (8.58 g, 171 mmol) at ambient temperature and the mixture was heated to reflux with stirring for 30 minutes. After cooling, hydrochloric acid (37%, 24 mL) was added to the mixture and the precipitate was filtered off. The filtrate was concentrated in vacuo and the residue was triturated with ethyl acetate to give
2-amino-1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)ethanone

hydrochloride (10.62 g, 64.5%) as a powder:
1H-NMR (300 MHz, DMSO-d6)δ3.72 (3H, s),5.18 (2H, s),6.24 (1H, br peak),6.96 (2H, d, J=8 Hz),7.10 (2H, d, J=8 Hz),7.24-7.50 (7H, m),8.00 (2H, d, J=8 Hz),8.77 (2H, br peak);
MS (ES+) m/e 348.16.

Preparation 4

To a mixture of triphenylphosphine (6.88 g, 26.2 mmol), iodine (6.66 g, 26.2 mmol) and triethylamine (5.31 g, 52.5 mmol) in dichloromethane (100 mL) were added a solution of N-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2,2-difluoroacetamide (5.58 g, 13.1 mmol) in dichloromethane (10 mL) at ambient temperature under nitrogen and the mixture was stirred at same temperature for 2days. The reaction mixture was evaporated in vacuo and partitioned between water and ethyl acetate. The organic layer was separated, washed with 1 N hydrochloric acid, water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was purified by silica gel column chromatography (n-hexane - ethyl acetate=3-1) and triturated with petroleum ether to give 5-[4-(benzyloxy)phenyl]-2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazole (3.43 g, 64.2%) as a powder:
1H-NMR (300 MHz, CDCl3)δ 3.84 (3H, s),5.10 (2H, s),6.70 (H, t, J=53 Hz),6.91 (2H, d, J=8 Hz),6.98 (2H, d, J=8 Hz),7.29-7.46 (5H, m),7.50-7.60 (4H, m).

Preparation 5

To a suspension of sodium hydride (60% in oil, 410 mg, 10.2 mmol) in N,N-dimethylformamide (5 mL) was added a solution of 4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol (2.5 g, 9.85 mmol) in N,N-dimethylformamide (20 mL) dropwise at 0℃ under nitrogen and the mixture was stirred at same temperature for 1 hour. Then ethylbromoacetate (1.64 g, 9.85 mmol) was added and stirred at same temperature for 3 hours. The reaction

mixture was poured into water and extracted with ethyl acetate. The organic layer washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized from a mixture of water and ethanol to give ethyl {4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetate (2.66 g, 83.7%) as crystals:
1H-NMR (300 MHz, CDCl3)δ1.31 (3H, t, J=7.5 Hz),3.85 (3H, s),4.28 (2H, q, J=7.5 Hz),4.66 (2H, s),6.69 (1H, t, J=53 Hz),6.88-6.95 (4H, m),7.54 (2H, d, J=8 Hz),7.58 (2H, d, J=8 Hz);
MS (ES+) m/e 404.13.

Preparation 6

To a suspension of 2-amino-1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)ethanone hydrochloride (1.56 g, 4.14 mmol) in dichloromethame (16 mL) were added triethylamine (503 mg, 4.97 mmol) and trifluoroacetic anhydride (1.04 g, 4.97 mmol) at 0℃ under nitrogen and the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was evaporated in vacuo and partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was triturated with hexane to give N-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2,2,2-trifluoroacetamide (1.20 g, 65.3%) as a powder:
1H-NMR (300 MHz, CDCl3)δ3.76 (3H, s),5.09 (2H, s),6.35 (1H, d, J=7 Hz),6.84 (2H, d, J=8 Hz),6.94 (2H, d, J=8 Hz),7.26-7.44 (7H, m),7.87-8.00 (3H, m);
MS (ES-) m/e 442.26.

Preparation 7

5-[5-[4-(Benzyloxy)phenyl]-2-(difluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine (830 mg, 2.03 mmol) and dry 20% palladium hydroxide on carbon (240 mg) in ethanol (8 mL) and cyclohexene

(4 mL) was stirred at reflux condition for 2 hour and cooled to room temperature. After filtration, the reaction mixture was evaporated in vacuo to give 4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol (630 mg, 97.8%) as a powder:
1H-NMR (300 MHz, DMSO-d6) δ 3.89 (3H, s), 6.86 (2H, d, J=9 Hz), 6.91 (1H, d, J=9 Hz), 7.30 (1H, t, J=53 Hz), 7.84 (1H, dd, J=9, 2 Hz), 8.36 (1H, d, J=2 Hz);
MS (ES+) m/e 319.11.

Preparation 8
To a solution of 4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenol (120 mg, 0.378 mmol) in N,N-dimethylformamide (2 mL) were added 2-chloroethanol (76.1 mg, 0.946 mmol), potassium iodide (157 mg, 0.946 mmol) and potassium carbonate (209 mg, 1.51 mmol) at ambient temperature and the mixture was stirred at 75℃ for 18 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid , water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane-ethyl acetate=2-3) to give 2-{4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethanol (52.6 mg, 38.5%) as an amorphous powder:
1H-NMR (300 MHz, CDCl3) δ 2.03 (1H, t, J=7 Hz), 3.85 (3H, s), 3.94-4.03 (2H, m), 4.13 (2H, t, J=5 Hz), 6.70 (1H, t, J=53 Hz), 6.92 (2H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.51-7.60 (4H, m);

Preparation 9
To a solution of 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol (203 mg, 0.56 mmol) and triethylamine (85 mg, 0.84 mmol) in dichloromethane (4 mL) was added methanesulfonyl chloride (86.3 mg, 0.84 mmol) at 0℃ under nitrogen and the mixture

was stirred at same temperature for 2 hours. The reaction mixture was evaporated in vacuo and the residue was partitioned between water and chloroform. The organic layer was separated, washed with 1mol/L hydrochloric acid , water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo to give 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate (247 mg, 100.1%) as an oil:
1H-NMR (300 MHz, CDCl3)δ3.11 (3H, s),3.97 (3H, s),4.29 (2H, t, J=5 Hz),4.60 (2H, t, J=5 Hz),6.70 (1H, t, J=53 Hz),6.78 (1H, d, J=8 Hz),6.94 (2H, d, J=8 Hz),7.55 (2H, d, J=8 Hz),7.82 (1H, dd, J=8,2 Hz),8.41 (1H, d, J=2 Hz); .

Preparation 10

To a solution of 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate (247 mg, 0.561 mmol) in N,N-dimethylformamide (5 mL) was added potassium phthalimide (156 mg, 0.841 mmol) at ambient temperature and the mixture was stirred at 60℃ for 18 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid , water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo to give 2-(2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione (260 mg, 94.3%) as an oil:
1H-NMR (300 MHz, CDCl3)δ3.96 (3H, s),4.13 (1H, t, J=7 Hz),4.27 (1H, t, J=7 Hz),6.69 (1H, t, J=53 Hz),6.76 (1H, d, J=8 Hz),6.91 (2H, d, J=8 Hz),7.79 (2H, d, J=8 Hz),7.70-7.81 (3H, m),7.84-7.91 (2H, m),8.39 (1H, d, J=2 Hz); .

Preparation 11

To a solution of 2-(2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-ox

azol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione (260 mg, 0.529 mmol) in acetonitrile (5 mL) was added hydrazine monohydrate (212 mg, 4.23 mmol) at ambient temperature and the mixture was stirred at 60℃ for 5 hours. After cooling, the precipitate was filtered off. The filtrate was concentrated in vacuo to give 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine (184 mg, 96.2%) as an oil:
1H-NMR (300 MHz, CDCl3)δ3.11 (2H, t, J=5 Hz),3.97 (3H, s),4.03 (2H, t, J=5 Hz),6.70 (1H, t, J=53 Hz),6.78 (1H, d, J=8 Hz),6.94 (2H, d, J=8 Hz),7.54 (2H, d, J=8 Hz),7.82 (1H, dd, J=8,2 Hz),8.43 (1H, d, J=2 Hz);
MS (ES+) m/e 362.13.

Preparation 12

To a solution of 4-[(4-methoxyphenyl)acetyl]benzonitrile (3.0 g, 11.9 mmol) in tetrahydrofuran (30 mL) was added pyridinium tribromide (3.82 g, 11.9 mmol) portionwise at ambient temperature under nitrogen and the mixture was stirred at same temperature for 1.5 hours. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with hexane to give 4-[bromo(4-methoxyphenyl)acetyl]benzonitrile (3.77 g, 95.6%) as a powder:
1H-NMR (300 MHz, CDCl3)δ3.81 (3H, s),6.24 (1H, s),6.91 (2H, d, J=8 Hz),7.44 (2H, d, J=8 Hz),7.75 (2H, d, J=8 Hz),8.06 (2H, d, J=8 Hz).

Preparation 13

To a solution of 4-[bromo(4-methoxyphenyl)acetyl]benzonitrile (500 mg, 1.51 mmol) in acetone were added acetoxyacetic acid (179 mg, 1.51 mmol) and cesium carbonate (493 mg, 1.51 mmol) at ambient temperature under nitrogen and the mixture was stirred at same temperature for 18 hours. The reaction mixture was evaporated in vacuo and the residue was partitioned between water and ethyl

acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid , water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane-ethyl acetate=2-1) to give 2-(4-cyanophenyl)-1-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate (337 mg, 60.6%) as an oil:
1H-NMR (300 MHz, CDCl3)δ2.15 (3H, s),3.85 (3H, s),4.74 (1H, d, J=16 Hz),4.82 (1H, d, J=16 Hz),6.87-6.96 (3H, m),7.58 (2H, d, J=9 Hz),7.68 (2H, d, J=9 Hz),7.90 (2H, d, J=9 Hz);
MS (ES-) m/e 366.15.

Preparation 14

To a solution of 1,2-bis(4-methoxyphenyl)-2-oxoethyl (benzyloxy)acetate (775 mg, 1.84 mmol) in acetic acid (14 mL) was added ammonium acetate (1.42 g, 18.4 mmol) at ambient temperature and the mixture was heated to reflux with stirring for 1 hour. After cooling, the reaction mixture was evaporated in vacuo and acetic acid was azeotropically removed with toluene. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was purified by silica gel column chromatography (n-hexane - ethyl acetate=4-1) and triturated with ethanol to give 2-[(benzyloxy)methyl]-4,5-bis(4-methoxyphenyl)-1,3-oxazole (300 mg, 40.5%) as a pale yellow powder:
1H-NMR (300 MHz, CDCl3)δ3.84 (6H, s),4.67 (2H, s),4.70 (2H, s),6.84-6.94 (4H, m),7.26-7.44 (5H, m),7.51 (2H, d, J=8 Hz),7.56 (2H, d, J=8 Hz);
MS (ES+) m/e 402.12.

Preparation 15

1-[4-(Benzyloxy)phenyl]-2-bromo-2-(6-methoxy-3-pyridinyl)-ethanone (21.2 g, 78.1%) was prepared from 1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)ethanone (22

g, 66 mmol) and pyridinium tribromide (23.2 g, 72.6mmol) in a similar manner to that of Preparation 1.
powder
1H-NMR (300MHz, CDCl3) δ3.95 (3H, s), 5.14 (2H, s), 6.26 (1H, s), 6.80 (1H, d, J=8 Hz), 7.02 (2H, d, J=8 Hz), 7.30-7.46 (5H, m), 7.92 (1H, dd, J=8,2 Hz), 8.01 (2H, d, J=8 Hz), 8.21 (1H, d, J=2 Hz);
MS (ES+) m/e 411.98, 413.95.

Preparation 16
2-[2-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione (20.0 g, 81.2%) was prepared from 1-[4-(benzyloxy)phenyl]-2-bromo-2-(6-methoxy-3-pyridinyl)-ethanone (21.2 g, 51.5 mmol) and potassium phthalimide (9.54 g, 51.3 mmol) in a similar manner to that of Preparation 2.
powder
1H-NMR (300 MHz, CDCl3) δ3.91 (3H, s), 5.07 (2H, s), 6.65-6.72 (2H, m), 6.93 (2H, d, J=8 Hz), 7.27-7.41 (5H, m), 7.66-7.78 (3H, m), 7.78-7.88 (4H, m), 8.26 (1H, d, J=2 Hz).

Preparation 17
2-Amino-1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-ethanone hydrochloride (2.67 g, 110%) was prepared from 2-[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione (3.0 g, 6.27 mmol) in a similar manner to that of Preparation 3.
1H-NMR (300 MHz, DMSO-d6) δ3.82 (3H, s), 5.18 (2H, s), 6.32 (1H, br peak), 6.85 (1H, d, J=8 Hz), 7.10 (2H, d, J=8 Hz), 7.26-7.50 (5H, m), 7.71 (1H, dd, J=8,2 Hz), 8.02 (2H, d, J=8 Hz), 8.40 (1H, d, J=2 Hz), 8.91 (2H, br peak); .

Preparation 18
N-[2-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-2,2,2-trifluoroacetamide (824 mg, 42%) was prepared from 2-amino-1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-ethanone hydrochloride (1.7 g, 4.42 mmol) and trifluoroacetic anhydride (1.21 g, 5.74 mmol) in a similar manner to that of

Preparation 6.

powder

1H-NMR (300 MHz, CDCl3) δ3.89 (3H, s), 5.10 (2H, s), 6.31-6.48 (1H, m), 6.68 (1H, d, J=8 Hz), 6.96 (2H, d, J=8 Hz), 7.26-7.45 (5H, m), 7.53 (1H, dd, J=8,2 Hz), 7.91 (2H, d, J=8 Hz), 8.26 (1H, d, J=2 Hz).

Preparation 19

5-[5-[4-(Benzyloxy)phenyl]-2-(trifluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine (607 mg, 79.1%) was prepared from 5-[5-[4-(benzyloxy)phenyl]-2-(trifluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine (800 mg, 1.8 mmol) in a similar manner to that of Preparation 4.

powder

1H-NMR (300 MHz, CDCl3) δ3.97 (3H, s), 5.11 (2H, s), 6.78 (1H, d, J=8 Hz), 7.00 (2H, d, J=8 Hz), 7.30-7.49 (5H, m), 7.54 (2H, d, J=8 Hz), 7.84 (1H, dd, J=8,2 Hz), 8.44 (1H, d, J=2 Hz);

MS (ES+) m/e 427.12.

Preparation 20

4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenol (423 mg, 88.4%) was prepared from 5-[5-[4-(benzyloxy)phenyl]-2-(trifluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine (607 mg, 1.42 mmol) in a similar manner to that of Preparation 7.

powder

1H-NMR (300 MHz, CDCl3) δ3.97 (3H, s), 6.81 (1H, d, J=8 Hz), 6.88 (2H, d, J=8 Hz), 7.49 (2H, d, J=8 Hz), 7.89 (1H, dd, J=8,2 Hz), 8.43 (1H, d, J=2 Hz);

MS (ES-) m/e 335.12.

Preparation 21

2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanol (305 mg, 65.8%) was prepared from 4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenol (410 mg, 1.22 mmol) and 2-chloroethanol (584 mg, 7.32 mmol) in a similar manner to that of Preparation 8.

powder
1H-NMR (300 MHz, CDCl3)δ1.99 (1H, t, J=7 Hz),3.97 (3H, s),3.99 (2H, dt, J=7,5 Hz),4.12 (1H, t, J=5 Hz),6.79 (1H, d, J=8 Hz),6.96 (2H, d, J=8 Hz),7.55 (2H, d, J=8 Hz),7.84 (1H, dd, J=8,2 Hz),8.44 (1H, d, J=2 Hz);
MS (ES+) m/e 381.08.

Preparation 22
2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate (355 mg, 99.8%) was prepared from
2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanol (295 mg, 0.776 mmol) in a similar manner to that of Preparation 9.
oil
1H-NMR (300 MHz, CDCl3)δ3.11 (3H, s),3.97 (3H, s),4.29 (2H, t, J=5 Hz),4.60 (2H, t, J=5 Hz),6.80 (1H, d, J=8 Hz),6.95 (2H, d, J=8 Hz),7.55 (2H, d, J=8 Hz),7.84 (1H, dd, J=8,2 Hz),8.41 (1H, d, J=2 Hz);
MS (ES+) m/e 459.03.

Preparation 23
2-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione (395 mg, 100%) was prepared from
2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate (355 mg, 0.774 mmol) and potassium phthalimide (125 mg, 1.16 mmol) in a similar manner to that of Preparation 10.
powder
1H-NMR (300 MHz, CDCl3)δ3.97 (3H, s),4.14 (2H, t, J=5 Hz),4.28 (2H, t, J=5 Hz),6.77 (1H, d, J=9 Hz),6.92 (2H, d, J=9 Hz),7.50 (2H, d, J=9 Hz),7.69-7.91 (5H, m),8.39 (1H, d, J=2 Hz);

Preparation 24
2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxaz

ol-5-yl]phenoxy}ethylamine (153 mg, 53.4%) was prepared from 2-(2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione (385 mg, 0.756 mmol) in a similar manner to that of Preparation 11.
oil
1H-NMR (300 MHz, CDCl3)δ3.11 (2H, t, J=5 Hz),3.97 (3H, s),4.03 (2H, t, J=5 Hz),6.79 (1H, d, J=8 Hz),6.95 (2H, d, J=8 Hz),7.54 (2H, d, J=8 Hz),7.84 (1H, dd, J=8,2 Hz),8.44 (1H, d, J=2 Hz); .

Preparation 25
To a solution of difluoroacetic acid (799 mg, 8.33 mmol) in tetrahydrofuran (8 mL) were added oxalyl chloride (1.06 g, 8.33 mmol) and N, N-dimethylformamide (1 drop) at 0℃ under nitrogen and the mixture was stirred at ambient temperature for 1 hour. The mixture was added to a mixture of 2-amino-1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-ethanone hydrochloride (2.67 g, 6.94 mmol) and triethylamine (2.11 g, 20.8 mmol) in dichloromethane (25 mL) at 0℃ and the reaction mixture was stirred at same temperature for 2 hours. The reaction mixture was evaporated in vacuo and partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was purified by silica gel column chromatography (n-hexane - ethyl acetate=3-1) to give N-[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxo-ethyl]-2,2-difluoroacetamide (1.25 g, 42.6%) as a powder:
1H-NMR (300 MHz, CDCl3)δ3.89 (3H, s),5.10 (2H, s),5.89 (1H, t, =53 Hz),6.40 (1H, d, J=8 Hz),6.68 (1H, d, J=8 Hz),6.96 (2H, d, J=8 Hz),7.31-7.42 (5H, m),7.53 (1H, dd, J=8,2 Hz),7.89-8.00 (3H, m),8.25 (1H, d, J=2 Hz) .

Preparation 26
5-[5-[4-(Benzyloxy)phenyl]-2-(difluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine (840 mg, 70.2%) was prepared from

N-[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-2,2-difluoroacetamide (1.25 g, 2.93 mmol) in a similar manner to that of Preparation 4.
powder
1H-NMR (300 MHz, CDCl3) δ3.97 (3H, s), 5.10 (2H, s), 6.70 (1H, t, J=53 Hz), 6.77 (1H, d, J=8 Hz), 7.00 (2H, d, J=8 Hz), 7.30-7.48 (5H, m), 7.54 (2H, d, J=8 Hz), 7.82 (1H, dd, J=8,2 Hz), 8.44 (1H, d, J=2 Hz);

Preparation 27
Ethyl {4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}acetate (830 mg, 105%) was prepared from 4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol (620 mg, 1.95 mmol) and ethyl bromoacetate (390 mg, 2.34 mmol) in a similar manner to that of Preparation 5.
powder
1H-NMR (300 MHz, CDCl3) δ1.32 (3H, t, J=7 Hz), 3.97 (3H, s), 4.28 (2H, q, J=7 Hz), 4.66 (2H, s), 6.69 (1H, t, J=53 Hz), 6.78 (1H, d, J=8 Hz), 6.94 (2H, d, J=8 Hz), 7.55 (2H, d, J=8 Hz), 7.80 (1H, dd, J=8,2 Hz), 8.42 (1H, d, J=2 Hz);
MS (ES+) m/e 405.11.

Preparation 28
2-[4-(Benzyloxy)phenyl]-2-bromo-1-(6-methoxy-3-pyridinyl)-ethanone (1.87 g, 100%) was prepared from 2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)ethanone (1.5 g, 4.5 mmol) in a similar manner to that of Preparation 12.
oil
1H-NMR (300 MHz, CDCl3) δ4.00 (3H, s), 5.06 (2H, s), 6.28 (1H, s), 6.78 (1H, d, J=9 Hz), 6.96 (2H, d, J=9 Hz), 7.29-7.50 (7H, m), 8.16 (1H, dd, J=9,2 Hz), 8.81 (1H, d, J=2 Hz);

Preparation 29
1-[4-(Benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-2-oxo-ethyl cyclopropanecarboxylate (1.72 g, 93.8%) was prepared from 2-[4-(benzyloxy)phenyl]-2-bromo-1-(6-methoxy-3-pyridinyl)-

ethanone (1.85 g, 4.39 mmol) and cyclopropanecarboxylic acid (378 mg, 4.39 mmol) in a similar manner to that of Preparation 13.
oil
1H-NMR (300 MHz, CDCl3)δ0.85-0.99 (2H, m),1.04-1.14 (2H, m),1.71-1.85 (1H, m),3.96 (3H, s),5.04 (2H, s),6.70 (1H, s),6.73 (1H, d, J=9 Hz),6.97 (2H, d, J=9 Hz),7.28-7.45 (7H, m),8.10 (1H, dd, J=9,2 Hz),8.78 (1H, d, J=2 Hz);
MS (ES+) m/e 418.18.

Preparation 30
5-{5-[4-(Benzyloxy)phenyl]-2-cyclopropyl-1,3-oxazol-4-yl}-2-methoxypyridine (1.14 g, 69.4%) was prepared from 1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-2-oxo-ethyl cyclopropanecarboxylate (1.72 g, 4.12 mmol) and ammonium acetate (2.54 g, 33 mmol) in a similar manner to that of Preparation 14.
powder
1H-NMR (300 MHz, CDCl3)δ1.03-1.11 (2H, m),1.11-1.20 (2H, m),2.06-2.19 (1H, m),3.95 (3H, s),5.08 (2H, s),6.74 (1H, d, J=9 Hz),6.95 (2H, d, J=9 Hz),7.30-7.48 (7H, m),7.80 (1H, dd, J=8,2 Hz),8.39 (1H, d, J=2 Hz);
MS (ES+) m/e 399.17.

Preparation 31
4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol (710 mg, 83.4%) was prepared from 5-{5-[4-(benzyloxy)phenyl]-2-cyclopropyl-1,3-oxazol-4-yl}-2-methoxypyridine (1.1 g, 2.76 mmol) in a similar manner to that of Preparation 7.
powder
1H-NMR (300 MHz, CDCl3)δ1.01-1.11 (2H, m),1.11-1.20 (2H, m),2.06-2.18 (1H, m),3.95 (3H, s),6.16 (1H, br peak),6.75 (1H, d, J=9 Hz),6.81 (2H, d, J=9 Hz),7.38 (2H, d, J=9 Hz),7.84 (1H, dd, J=9,2 Hz),8.38 (1H, d, J=2 Hz);
MS (ES+) m/e 309.14.

Preparation 32

A mixture of 2-[(benzyloxy)methyl]-4,5-bis(4-methoxyphenyl)-1,3-oxazole (88 mg, 0.219 mmol) and 10% palladium on carbon (20 mg) in a mixture of methanol (2 mL) and tetrahydrofuran (2 mL) was stirred at ambient temperature under hydrogen for 6 hours. The reaction mixture was filtered through Celite and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane - ethyl acetate=1-1) and triturated with a mixture of hexane and diethyl ether to give [4,5-bis(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol (44 mg, 65.4%) as a pale yellow powder.

1H-NMR (300 MHz, CDCl3) δ 2.36 (1H, t, J=7 Hz), 3.84 (6H, s), 4.79 (2H, d, J=7 Hz), 6.85-6.94 (4H, m), 7.51 (2H, d, J=8 Hz), 7.56 (2H, d, J=8 Hz);

MS (ES+) m/e 312.13

Preparation 33

To a solution of 4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol (40 mg, 0.126 mmol) in N,N-dimethylformamide (1 mL) were added 3-bromo-1-propanol (26.3 mg, 0.189 mmol) and potassium carbonate (52.3 mg, 0.378 mmol) at ambient temperature and the mixture was stirred at same temperature for 18 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane-ethyl acetate=1-1) to give 3-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}-1-propanol (25 mg, 52.8%) as an oil.

1H-NMR (300 MHz, CDCl3) δ 1.64 (1H, br peak), 2.01-2.14 (2H, m), 3.84 (3H, s), 3.88 (2H, t, J=5 Hz), 4.16 (2H, t, J=5 Hz), 6.69 (1H, t, J=53 Hz), 6.88-6.95 (4H, m), 7.50-7.60 (4H, m);

MS (ES+) m/e 376.07.

Preparation 34

4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol (2.75 g, 103.2%) was prepared from 5-[4-(benzyloxy)phenyl]-2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazole (3.42 g, 8.39 mmol) in a similar manner to that of Preparation 32.

powder

1H-NMR (300 MHz, CDCl3) δ 3.84 (3H, s),5.27 (1H, s),6.70 (1H, t, J=53 Hz),6.85 (2H, d, J=8 Hz),6.92 (2H, d, J=8 Hz),7.51 (2H, d, J=8 Hz),7.56 (2H, d, J=8 Hz);

MS (ES-) m/e 316.19.

Preparation 35

4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetonitrile (241 mg, 71.5%) was prepared from 4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol (300 mg, 0.946 mmol) and iodoacetonitrile (316 mg, 1.89 mmol) in a similar manner to that of Preparation 33.

1H-NMR (300 MHz, CDCl3) δ 3.85 (3H, s),4.82 (2H, s),6.71 (1H, t, J=53 Hz),6.94 (2H, d, J=8 Hz),7.00 (2H, d, J=8 Hz),7.55 (2H, d, J=8 Hz),7.64 (2H, d, J=8 Hz).

Preparation 36

To a solution of {4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetonitrile (245 mg, 0.688 mmol) in tetrahydrofuran (2 mL) was added lithium aluminum hydride (31.3 mg, 0.825 mmol) at 0℃ under nitrogen and the mixture was stirred at same temperature for 3 hours. To the reaction mixture was added water dropwise at 0℃. The precipitate was removed by vacuum filtration and the filtrate was evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was dissolved in dichloromethane (2 mL). To a solution were added triethylamine (83.5 mg, 0.115 mmol) and di-tert-butyl dicarbonate (180 mg, ,

0.115 mmol) 0℃ and the mixture was stirred at same temperature for 2 hours. The reaction mixture was evaporated in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (ethyl acetate-n-hexane=1-1) to give tert-butyl 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate (94 mg, 29.7%) as an oil.

1H-NMR (300 MHz, CDCl3) δ 1.46 (9H, s),3.56 (2H, q, J=5 Hz),3.85 (3H, s),4.06 (2H, t, J=5 Hz),4.99 (1H, br peak),6.70 (1H, t, J=53 Hz),6.88-6.95 (4H, m),7.51-7.59 (4H, m);
MS (ES+) m/e 461.15.

Preparation 37

4N hydrogen chloride solution in ethyl acetate (0.5 mL) was added to a solution of 1-tert-butyl 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate (92 mg, 0.2 mmol) in ethyl acetate (1 mL) at ambient temperature. The mixture was stirred at same temperature for 3 hours. After evaporation of solvent, the residue was triturated with ether to give 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanamine hydrochloride (52 mg, 65.6%) as an amorphous powder.

1H-NMR (300 MHz, DMSO-d6) δ 3.24 (2H, br peak),3.79 (3H, s),4.23 (2H, t, J=5 Hz),7.00 (2H, d, J=8 Hz),7.10 (2H, d, J=8 Hz),7.31 (1H, t, J=53 Hz),7.50 (2H, d, J=8 Hz),7.55 (2H, d, J=8 Hz),8.09 (3H, br peak);
MS (ES+) m/e 361.13.

Example 1

To a solution of ethyl {4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetate (4.3 g, 10.7 mmol) in a mixture of diethyl ether

(40 mL) and tetrahydrofuran (10 mL) was added lithium aluminum hydride (405 mg, 10.7 mmol) portionwise at 0℃ under nitrogen and the mixture was stirred at same temperature for 3 hours. To the reaction mixture was added water dropwise at 0℃. The precipitate was removed by vacuum filtration and the filtrate was evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid , water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane-ethyl acetate=2-1) and crystallized from a mixture of ethyl acetate and hexane to give 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol as white crystals:

mp114-116℃;

1H-NMR (300 MHz, CDCl3) δ 2.02 (1H, t, J=7 Hz),3.85 (3H, s),3.98 (2H, td, J=5, 7 Hz),4.12 (2H, t, J=5 Hz),6.70 (1H, t, J=52 Hz),6.91 (2H, d, J=8 Hz),6.94 (2H, d, J=8 Hz),7.52-7.60 (4H, m);

MS (ES+) m/e 362.13.

Example 2

To a solution of 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanamine (136 mg, 0.377 mmol) in dichloromethane (3 mL) was added trimethylsilyl isocyanate (87 mg, 0.755 mmol) at ambient temperature and the mixture was stirred at same temperature for 24 hours. The reaction mixture was poured into water and extracted with chloroform. The organic layer washed with 1mol/L hydrochloric acid , water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform-methanol=10-1) to give N-(2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea (95 mg, 62.4%) as an amorphous powder:

mp: 146-149℃;

1H-NMR (300 MHz, DMSO-d6)δ3.25-3.40 (2H, m),3.80 (3H, s),4.00 (2H, t, J=7 Hz),5.54 (2H, s),6.17 (1H, t, J=7 Hz),7.00 (2H, d, J=8 Hz),7.06 (2H, d, J=8 Hz),7.29 (1H, t, J=53 Hz),7.47-7.55 (4H, m).

Example 3

N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea (52 mg, 59.6%) was prepared from 2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine (79.3 mg, 0.201 mmol) in a similar manner to that of Example 2.

powder

1H-NMR (300 MHz, CDCl3-CD3OD/10-1)δ3.58 (2H, t, J=5 Hz),3.97 (3H, s),4.07 (2H, t, J=5 Hz),6.81 (2H, d, J=8 Hz),6.95 (2H, d, J=8 Hz),7.53 (2H, d, J=8 Hz),7.85 (1H, dd, J=8,2 Hz),8.40 (1H, d, J=2 Hz);

MS (ES+) m/e 423.15.

Example 4

2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol (630 mg, 82.2%) was prepared from ethyl {4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}acetate (855 mg, 2.11 mmol) in a similar manner to that of Example 1.

crystals

m p 126-128℃;

1H-NMR (300 MHz, CDCl3) δ 2.01 (1H, t, J=6 Hz),3.98 (3H, s),4.00 (2H, dd, J=6,5 Hz),4.13 (2H, t, J=5 Hz),6.70 (1H, t, J=53 Hz),6.77 (1H, d, J=8 Hz),6.95 (2H, d, J=8 Hz),7.55 (2H, d, J=8 Hz),7.82 (1H, dd, J=8,2 Hz),8.43 (1H, d, J=2 Hz);

MS (ES+) m/e 363.14.

Example 5

2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol (575 mg, 71.9%) was prepared from

4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol (700 mg, 2.27 mmol) and 2-chloroethanol (1.1 g, 13.6 mmol) in a similar manner to that of Preparation 8.

powder

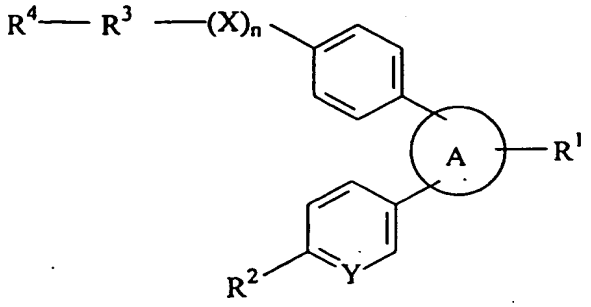
1H-NMR (300 MHz, CDCl3) δ1.02-1.11 (2H, m), 1.11-1.20 (2H, m), 2.02 (1H, t, J=6 Hz), 2.06-2.17 (1H, m), 3.95 (3H, s), 3.98 (2H, t, J=5 Hz), 4.10 (2H, t, J=5 Hz), 6.74 (1H, d, J=9 Hz), 6.90 (2H, d, J=9 Hz), 7.44 (2H, d, J=9 Hz), 7.79 (1H, dd, J=9,2 Hz), 8.38 (1H, d, J=2 Hz);

MS (ES+) m/e 353.19.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFININING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I):



(I)

wherein R^1 is lower alkyl which is optionally substituted with suitable substituent(s), cyclo(lower)alkyl, lower alkynyl, cyano, acyl, or N,N-di(lower)alkylcarbamoyl;

R^2 is lower alkyl, lower alkoxy, cyano or 1H-pyrrol-1-yl;

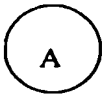
R^3 is lower alkylene or lower alkenylene;

R^4 is hydroxy, protected hydroxy, amino, protected amino, carboxy, protected carboxy, acyl, or cyano;

X is O, S, SO or SO_2;

Y is CH or N;

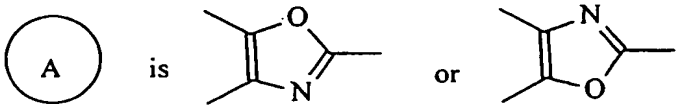
n is 0 or 1; and



is a N and O-containing heterocyclic group;

or salts thereof.

2. The compound of Claim 1, wherein



3. A pharmaceutical composition comprising the compound (I) or its salts of Claim 1, as an active ingredient, in association with a pharmaceutically non-toxic carrier or excipient.

4. A compound of Claim 1 for use as a medicament

5. A method for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases which comprises administering an effective amount of the compound or its salts of Claim 1 to human beings or animals.

6. Use of the compound of Claim 1 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases in human beings or animals.

7. The analgesic agent comprising the compound of Claim 1, which is usable for treating and/or preventing pains caused by or associated with acute or chronic inflammations without causing gastrointestinal disorders.

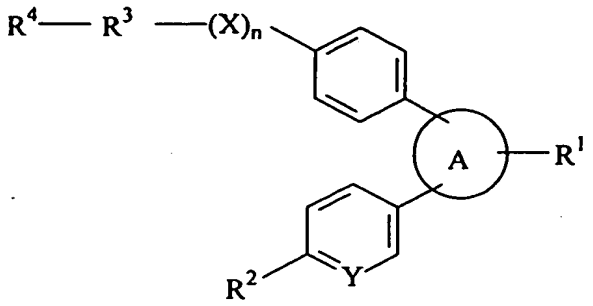
8. The analgesic agent of Claim 7, which is usable for treating or preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, or juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury without causing gastrointestinal disorders.

9. A commercial package comprising the pharmaceutical composition containing the compound (I) identified in Claim 1 and a written matter associated therewith, wherein the written matter states that the compound (I) can or should be used for preventing or treating inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases.

DATED this 17th day of January 2003
Fujisawa Pharmaceutical Co., Ltd.
By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

A B S T R A C T

A compound of the formula (I):



(I)

wherein R^1 is lower alkyl which is optionally substituted with suitable substituent(s), cyclo(lower)alkyl, lower alkynyl, cyano, acyl, or N,N-di(lower)alkylcarbamoyl;

R^2 is lower alkyl, lower alkoxy, cyano or 1H-pyrrol-1-yl;

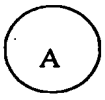
R^3 is lower alkylene or lower alkenylene;

R^4 is hydroxy, protected hydroxy, amino, protected amino, carboxy, protected carboxy, acyl, or cyano;

X is O, S, SO or SO_2;

Y is CH or N;

n is 0 or 1; and



is a N and O-containing heterocyclic group;

or salts thereof, which are useful as a medicament.